Vulvar ulcers as a rare manifestation of hematologic malignancy

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INTRODUCTION

Vulvar ulcers have a wide differential diagnosis. They are most commonly caused by infections (particularly sexually transmitted ones),[1-5] with inflammatory conditions (such as Behçet and Crohn disease) and neoplastic lesions (mainly squamous cell carcinoma) explaining most of the remaining cases, but a definitive diagnosis may remain elusive.[1-5] Neutrophilic dermatoses, such as Sweet's syndrome and pyoderma gangrenosum, are inflammatory skin disorders characterized by the infiltration of neutrophils in the absence of infection.[6,7] Sweet syndrome often presents with acute-onset tender nodules and plaques, commonly on the upper extremities, whereas pyoderma gangrenosum frequently consists of a painful ulcer with an undermined border on the lower limbs. Both conditions are clinically pleomorphic, but oral and genital lesions are rare.[6,7] They are often associated with underlying systemic diseases, particularly hematologic malignancies such as acute myeloid leukemia and myelodysplastic syndromes.[6-8] We report the challenging case of a 57-year-old female who presented with fever and painful vulvar lesions, which were found to be the first clinical manifestation of a paraneoplastic neutrophilic dermatosis related to a hematologic malignancy.

CASE REPORT

A 57-year-old female presented to the Emergency Department with a history of fever and painful vulvar lesions with 1 week duration with no improvement after 6 days of oral doxycycline 200 mg daily. She also reported mild migratory polyarthralgia since 1 month but denied other systemic symptoms. She had been previously healthy, with no past medical history besides dyslipidemia treated with atorvastatin. On physical examination, she was febrile (38.0°C) but hemodynamically stable. The patient presented with multiple ulcerative lesions, predominantly located on the labia majora and inner thighs. These lesions exhibited violaceous borders and a friable vegetating center, occurring on a background of indurated vulvar edema (Fig 1). Lesions measured between 0.5 to 3 cm in size, with some demonstrating infiltrated borders and superficial skin detachment at the periphery. There were also multiple millimetric shallow oral ulcers on an erythematous base (Fig 2) located on the hard palate and gingivae. The serum biochemistry profile revealed elevated C-reactive protein of 36.50 mg/dL ($N < 0.50$ mg/dL), procalcitonin 1.10 ($N < 0.5$ ng/dL), and D-dimers of 71,148 ng/mL ($N < 500$ ng/mL), and the complete blood count a pronounced leukocytosis of 40.8 $\times$ 10^9/L (N 3.9 - 10.2 $\times$ 10^9/L), mild normocytic anemia of 11.0 g/dL (N 12.0 $-$ 15.6 g/dL) and moderate thrombocytopenia of 67 $\times$ 10^9/L (N 150 $-$ 400 $\times$ 10^9/L). Serologic tests for syphilis, hepatitis B and C virus, and human immunodeficiency virus were negative,

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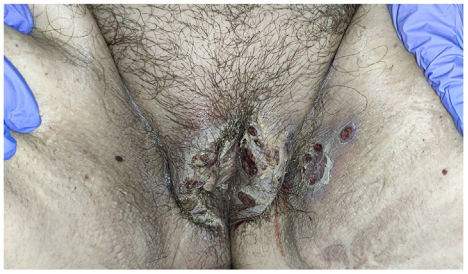

Fig 1. Multiple indurated vulvar ulcers on the labia majora and inner thighs with violaceous and partially detached borders, with concomitant vulvar edema.

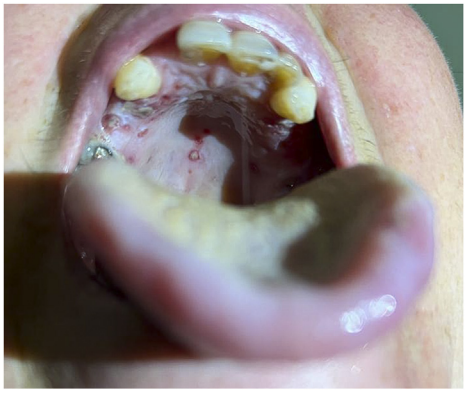

Fig 2. Millimetric oral ulcers on an erythematous base on the hard palate and gingivae.

as were polymerase chain reaction tests in urine for detection of *N. gonorrhoeae* and *C. trachomatis* and polymerase chain reaction for cytomegalovirus from the base of a vulvar ulcer. Repeated peripheral blood cultures were negative. The patient was admitted to the dermatology ward for etiologic investigation and treatment. The initial working diagnoses were pemphigus vulgaris and Behçet disease, in coexistence with a herpes simplex virus infection of the oral mucosa and a possible leukemoid reaction to an underlying systemic infectious process. She was started on empiric intravenous meropenem 1g t.i.d. plus clindamycin 600 mg q.i.d., oral acyclovir 400 mg t.i.d., and oral methylprednisolone 32 mg daily, with complete resolution of the oral lesions in 1 week, but not of the vulvar ulcers. Repeated immunophenotyping of the peripheral blood revealed a relative increase of the granulocyte lineage, mainly neutrophils, with no increased blasts, compatible with a reactive process. Histopathologic analysis of a skin biopsy of these persistent vulvar lesions revealed a dense infiltrate composed of mature neutrophils in both dermis and focally in the hypodermis, with no atypical granulocytes nor blastic cells, which was consistent with neutrophilic dermatosis within the

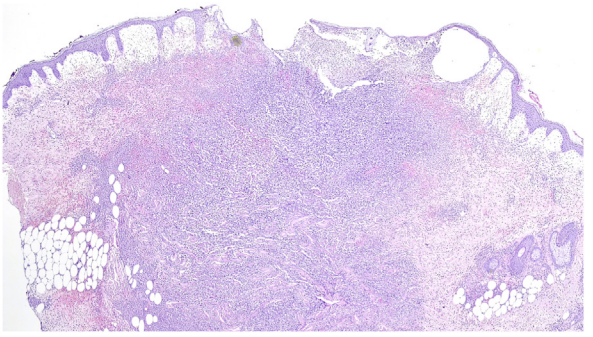

Fig 3. Histopathologic examination (H&E 40×) of a skin biopsy of the edge of a vulvar ulcer demonstrating a dense neutrophilic infiltrate in both dermis and focally in the hypodermis with absence of vasculitis.

spectrum of Sweet syndrome and pyoderma gangrenosum (Fig 3). Skin biopsy for direct immunofluorescence revealed a granular deposition of complement 3 in the dermoepidermal junction. Indirect immunofluorescence in serum for antibodies anti-bullous pemphigoid-180, anti-bullous pemphigoid-230, anti-desmoglein 1 and 3 were negative. Antinuclear antibodies and human leukocyte antigen-B 51 were also negative. During the hospital stay, the patient developed severe anemia (hemoglobin 7.1 g/dL) and thrombocytopenia (platelets 28 × 10^9/L), both requiring transfusional support. She was transferred to the Hematology ward and underwent bone marrow aspiration and biopsy that revealed 26% of myeloid blasts and presence of the translocation (15;17) in the malignant cells, establishing the diagnosis of non–high-risk classic acute promyelocytic leukemia. Treatment was promptly initiated with all-trans retinoic acid plus arsenic trioxide chemotherapy, comprising an induction plus consolidation protocol with weekly infusions over a 6-month period. Complete resolution of the vulvar lesions (Fig 4) and hematologic abnormalities was observed after 2 months of therapy. In order to facilitate the resolution of the cutaneous lesions, oral prednisone at a dose of 0.5 mg/kg per day was administered orally, with a gradual reduction in dosage over a period of 6 months. The patient is currently in remission, 3 months after the completion of all-trans retinoic acid plus arsenic trioxide therapy.

DISCUSSION

Multiple vulvar lesions are most frequently found in the setting of sexually transmitted infections but pose a diagnostic challenge once these are excluded.[1-5] A complete clinical history and physical examination are determinant to focus the search for a

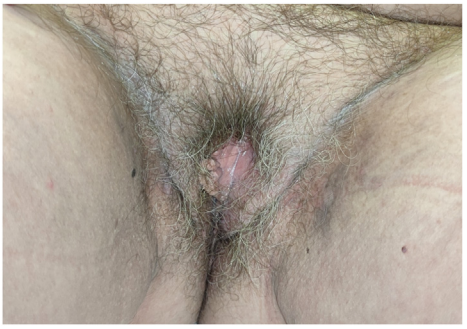

Fig 4. Complete resolution of the vulvar ulcers with slight local postinflammatory hyperpigmentation after treatment.

cause.[2,4,5] Nevertheless, when the diagnosis is still unclear, complementary examinations, including a skin biopsy, can be of uttermost importance.[2,4] In our patient, histopathologic analysis of the vulvar ulcers revealed a neutrophilic dermatosis in the spectrum of Sweet syndrome and pyoderma gangrenosum that, in the setting of persistent hematologic abnormalities, prompted continued investigation for an underlying hematologic malignancy. Acute promyelocytic leukemia is a subtype of acute myeloid leukemia which mostly presents with pancytopenia or a life-threatening coagulopathy.[8] A paraneoplastic neutrophilic dermatosis consisting of vulvar lesions has only been rarely reported in association with acute promyelocytic leukemia[9,10] but was, in this case, an important diagnostic clue that enabled timely treatment. Drug induced ulcers should also be considered, such as in the context of all-trans retinoic acid therapy. However, timing and response to therapy are helpful to differentiate both conditions. To conclude, interdisciplinary evaluation was essential to help determine the cause of the vulvar ulcers in our patient and, ultimately, to guide adequate treatment.

Conflicts of interest

None disclosed.

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